REMARKS/ARGUMENTS

Claims 1-5 and 8-13 are pending in this application after entry of this Amendment. Claims 6 and 7 are canceled, Claims 1, 5, and 8 are amended herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. The claims are amended to clarify the subject matter Applicants regard as their invention. No new matter has been added.

Claim 13 has been added. Applicants believe that this claim is patentable over the cited art.

The claims stand rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. 103(a) as being obviousness over three separate combinations of references.

A. Rejection of Claims under 35 U.S.C. § 112, first paragraph

1.) Rejection of Claims 5 and 8.

The Office action states that Claims 5 and 8 are rejected under 35 U.S.C. § 112, first paragraph because the term "excluding cyclophosphamide" constitutes new matter in that the term is not disclosed or taught in the specification.

Applicants have amended Claims 5 and 8 to remove the term "excluding cyclophosphamide." Claims 5 and 8 as currently amended contain only terms taught or disclosed in the specification.

2.) Rejection of Claims 1, 4-5 and 7-12.

The Office action states that Claims 1, 4-5 and 7-12 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Office action states that prodrugs were not described in the specification in such a way as to enable one skilled in the art to make or use the invention.

Applicants have amended Claim 1 to remove prodrugs from the scope of the claim. Applicants note that the amendment of Claim 1 also removes prodrugs from the scope of Claims

4-5 and 7-12 because these Claims are dependent upon Claim 1. The term "prodrugs" does not appear in any of pending Claims 4, 5 and 8-12. Claim 7 is cancelled herewith.

3.) Rejection of Claim 7.

The Office action states that Claim 7 is rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Applicants have cancelled Claim 7 in the present amendments. Accordingly, this rejection is moot.

B. <u>Rejection of Claims under 35 U.S.C. § 103(a)</u>

1.) Rejection of Claims 1-3 over Hilgard et al. Cancer Chemother. Phamacol., (1993) 32:90-95 ("Hilgard") in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition ("Calabresi").

The Hilgard reference discloses the use of miltefosine in combination with cyclophosphamide for the treatment of mammary carcinoma, and discloses by reference the combination of miltefosine with cisplatin derivatives. This reference does not teach any other combinations.

The Calabresi reference teaches that single-agent chemotherapy can lead to the outgrowth of cancer cells that are resistant to the chemotherapeutic (see page 1230). The Calabresi reference further teaches that there are a variety of mechanisms by which tumor cells acquire drug resistance (page 1230, 2nd paragraph), and that drugs are generally more effective in combination and may be synergistic through biochemical interactions. The Calabresi reference explains that in designing drug regimens for clinical use, it is desirable to use drugs that do not share common mechanisms of resistance and that do not overlap in their major toxicities (see page 1230).

The Calabresi reference also teaches that single-agent chemotherapy can lead to the outgrowth of cancer cells that are resistant to the chemotherapeutic (see page 1230). The Calabresi reference further teaches that there are a variety of mechanisms by which tumor cells acquire drug resistance (page 1230, 2nd paragraph), and that drugs are generally more effective in

combination and may be synergistic through biochemical interactions. The Calabresi reference explains that in designing drug regimens for clinical use, it is desirable to use drugs that do not share common mechanisms of resistance and that do not overlap in their major toxicities (see page 1230).

The Office action states that Hilgard teaches the use of the compounds of formulae I and II combined with a conventional platinum complex for the treatment of mammary carcinoma. The Office action also states that Calabresi teaches that adjuvant therapy is commonly used in treating breast cancer, and that certain classes of antineoplastic agents are used for treatment of breast cancer. The Office action states that substituting other platinum complexes for cisplatin as taught by Hilgard would be obvious.

Applicants again argue that not every combination of drugs will be effective against all types of tumor. Indeed, one may infer from the teaching of the Calabresi reference that two compounds that are individually useful for treating a particular cancer type would not be useful in combination if they share common mechanisms of resistance or if they overlap in their major toxicities. Although the Calabresi reference teaches that a properly selected combination may be useful, it provides no specific direction as to selecting a particular combination for mammary carcinoma, or for any other tumor type. Absent an understanding of the mechanisms of drug resistance and drug activity, one of ordinary skill in the art would have no obvious way of selecting effective combinations of alkylphosphocholines and other antitumor agents. Even within a class of drugs (e.g. cisplatin and cisplatin analogs) there will be differences in resistance mechanisms, efficacy, and side effects profiles. Accordingly, use of the combinations of claims 1-3 would not have been obvious to a person of ordinary skill in the art at the time that the claimed invention was made.

At least by virtue of the remarks set forth above, Applicants respectfully submit that claims are patentable over the cited art.

2.) Rejection of Claims 1-5 and 7-12 over Hilgard et al., Cancer Chemother. Pharmacol., (1993) 32: 90-95 ("Hilgard") in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition ("Calabresi"), in further view of

Hilgard et al., Advances in Experimental Medicine and Biology, (1996) 157-164 ("Hilgard II"), and in further view of Principe et al. Anti-Cancer Drugs (1992), 3, 577-587 ("Principe").

The teachings of Hilgard and Calebresi have been set forth in the discussion above.

The Hilgard II reference teaches that D-21266 can be used in combination with cyclophosphamide, adriamycin, or cisplatin.

The Principe reference teaches the combination of four particular ether phospholipids with various antineoplastic agents.

The Office action states the combination of the cited references would motivate one of ordinary skill in the art to administer combination therapy comprising alkylphospholipids and other antineoplastic agents, and that one of ordinary skill in the art would have a reasonable expectation of success in doing so.

Applicants again argue that not every combination of drugs will be effective against all types of tumor. Indeed, one may infer from the teaching of the Calabresi reference that two compounds that are individually useful for treating a particular cancer type would not be useful in combination if they share common mechanisms of resistance or if they overlap in their major toxicities. Although the Calabresi reference teaches that a properly selected combination may be useful, it provides no specific direction as to selecting a particular combination for mammary carcinoma, or for any other tumor type. Absent an understanding of the mechanisms of drug resistance and drug activity, one of ordinary skill in the art would have no obvious way of selecting effective combinations of alkylphosphocholines and other antitumor agents. Even within a class of drugs (e.g. cisplatin and cisplatin analogs) there will be differences in resistance mechanisms, efficacy, and side effects profiles in different tumor types.

The Principe reference bears this out. In the second paragraph on page 581of Principe, the authors teach that in HT29 cells, a supra-additive effect is observed with the combination of ether phospholipid ET-18-OCH_3 and MMC, ADM, CDDP, BLM, VLB, and VP-16. However, in A427 cells, supra-additive effect is observed with the combination of ether phospholipid ET-

18-OCH_3 and MMC, ADM, CDDP, BLM, or VLB, but a sub-additive effect is observed with the combination of ether phospholipid ET-18-OCH_3 and VLB or VP-16. These differences show that whether a synergistic result is obtained depends on both the cell type and on the specific agents used. One cannot reliably predict how a particular cell type will react to a particular combination of agents. Accordingly, use of the combinations of claims 1-5 and 7-12 would not have been obvious to a person of ordinary skill in the art at the time that the claimed invention was made.

Applicants note that Claim 7 has been cancelled in the present amendment. Accordingly, the arguments made above are moot with respect to Claim 7.

3.) **Rejection of Claims 2, 7, and 10 over Hilgard et al. Cancer Chemother. Phamacol, (1993) 32:90-95 ("Hilgard") in view of Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374 ("Stekar").**

The Hilgard reference discloses the use of miltefosine in combination with cyclophosphamide for the treatment of mammary carcinoma, and discloses by reference the combination of miltefosine with cisplatin derivatives. This reference does not teach any other combinations.

The Stekar reference discloses the treatment of mammary carcinoma with a two week oral dosing of miltefosine followed by an injection of cyclophosphamide. This reference does not teach any other combinations.

The Office action states that the combination of miltefosine with cisplatin showed considerable synergy, and that a combination of miltefosine and cisplatin is within the claim limitation. The Office action also states that one of ordinary skill in the art would expect other platinum drugs to demonstrate similar synergy. The Office action also states that the combination of miltefosine with other antitumor agents would be obvious as a result of the combination of the teachings of Hilgard and Stekar.

Applicants note first that Claim 7 has been cancelled in the current amendments.

Applicants note second that neither cisplatin nor any other platinum based antitumor drug is within the scope of Claim 2. Moreover, as discussed with respect to the Principe reference above, whether a synergistic result is obtained depends on both the cell type and on the specific agents used. Accordingly, one cannot infer that synergy will be observed using the combinations of Claim 2 based on the combination of miltefosine with cisplatin.

As to the synergy observed with cisplatin making the use of other platinum agent obvious, applicants again refer to the discussion of the Principe reference above. Principe demonstrates that whether a synergistic result is obtained depends on both the cell type and on the specific agents used. One cannot reliably predict how a particular cell type will react to a particular combination of agents. Accordingly, use of the combinations of claims 2 and 10 would not have been obvious to a person of ordinary skill in the art at the time that the claimed invention was made.

At least by virtue of the remarks set forth above, Applicants respectfully submit that all pending claims are patentable over the cited art.

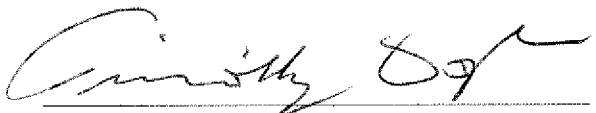
CONCLUSION

Based on the foregoing amendments and remarks, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicants,



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